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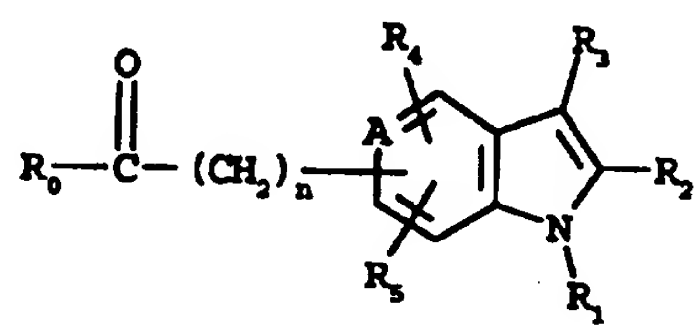
(54) Title: COMBINATORIAL SOLID PHASE SYNTHESIS OF A LIBRARY OF INDOLE DERIVATIVES

(57) Abstract

A process for preparing libraries of indole derivatives of formula (I) by solid phase synthesis in the presence of organometallic catalysts. The resulting compound libraries have a very high purity degree, which allows biological testing on the crude products with a high confidence degree, without any cross contaminations.



(I)

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COMBINATORIAL SOLID PHASE SYNTHESIS OF A LIBRARY OF INDOLE DERIVATIVES.

The present invention relates to a process for the generation of a plurality (library) of different indole derivatives, and to the use of said library to search for novel classes of compounds and individual compounds possessing selected properties for pharmaceutical applications.

Recently there has been an ever-increasing demand for chemical compounds that selectively act at specific biological recognition sites. These compounds can be used, inter alia, as inhibitors, activators or modulators of enzymes, as receptor ligands (agonists, antagonists or modulators), or for marking. To this purpose, methods have been developed to simultaneously synthesize a multiplicity (library) of different compounds and to assay them. These libraries (combinatorial compound libraries) usually consist of natural or modified aminoacids or nucleotides, and the like. The individual different ligands of these libraries are normally synthesized in parallel, either as mixtures or as physically separated individuals. These parallel syntheses make it possible to produce libraries containing a very large number of different ligands over a short period of time.

Also some libraries of small organic compounds have been synthesized, but the nature of the basic molecular backbone (scaffold) is mainly limited to aromatic and alicyclic compounds. Only some heterocyclic scaffolds have been synthesized. On the other hand, a large number of pharmacologically active compounds include heterocycles, and namely benzofused heterocyclic compounds. Therefore, there is

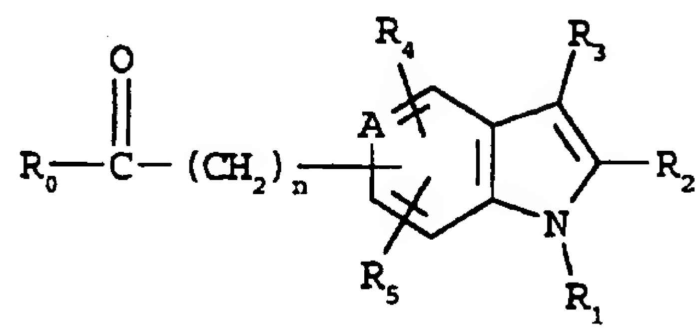
still the need for new heterocyclic scaffolds to be synthesized and tested by means of combinatorial chemistry.

These libraries of small organic compounds are often synthesized on solid phase by using suitable resins and linkers. However, for this purpose a limited number of reactions is available, if compared with the number of organic reactions known in literature. Particularly, the use of organometallic catalysts in solid phase syntheses (SPS) is very limited, since many difficulties are encountered. For instance, the metal often separates at the reaction end contaminating the final products. Moreover, additives are usually added to the reaction medium which remain in suspension and contaminate the final products.

We have now surprisingly found that it is possible to synthesize in solid phase arrays of indole derivatives of formula (I) as reported hereinbelow, by using organometallic catalysts. The use of solid phase synthesis allows purification of the final product from excess reagents and catalysts by simple washing. Moreover, it is possible to employ mild reaction conditions during the whole reaction, obtaining high yields and high purity degrees. It is to be noted that purity is very important in combinatorial chemistry, since the obtained arrays are usually tested as such, without any purification. Therefore, a low purity degree of the final products can be very harfmul for biological testing. We have surprisingly found that the compound libraries generated by the instantly claimed process have a very high purity degree (typically, 85-95% by HPLC assay), which allows biological testing on the crude products with a high confidence degree, without any cross

contaminations.

Therefore, a first object of the present invention is a process for preparing a plurality (library) of indole derivatives of formula:



(I)

wherein:

R_1, R_2, R_3, R_4, and R_5 are, each independently, hydrogen or a structural diversity element, with the proviso that at least one of R_1, R_2, R_3, R_4, and R_5 is different from hydrogen;

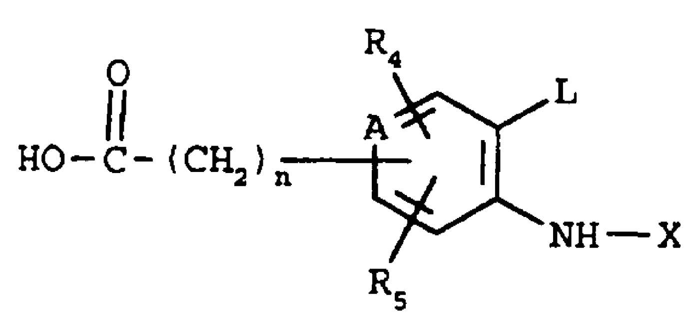
R_0 is $-NR_6R_7$ or $-OR_8$, wherein R_6, R_7, and R_8 are, each independently, hydrogen or a structural diversity element;

A is CH or N, and may be in any of the unsubstituted positions of the phenyl ring; and

n is zero or an integer from 1 to 4;

said process comprising the steps of:

(a) coupling to a solid support a first scaffold of formula:



(II)

wherein:

R_4 and R_5 are, each independently, hydrogen or a structural diversity element;

A is CH or N, and may be in any of the unsubstituted positions of the phenyl ring;

n is zero or an integer from 1 to 4;

L is a leaving group; and

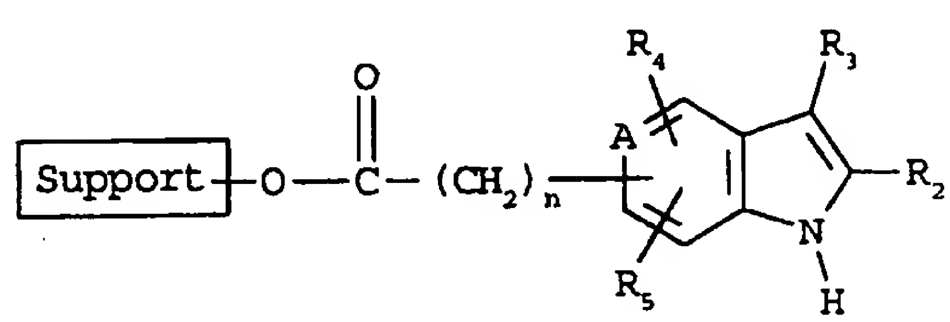
X is hydrogen or an activating group;

(b) reacting said first scaffold coupled to the solid support with a second scaffold of formula:

$$R_2-C \equiv C-R_3 \qquad (III)$$

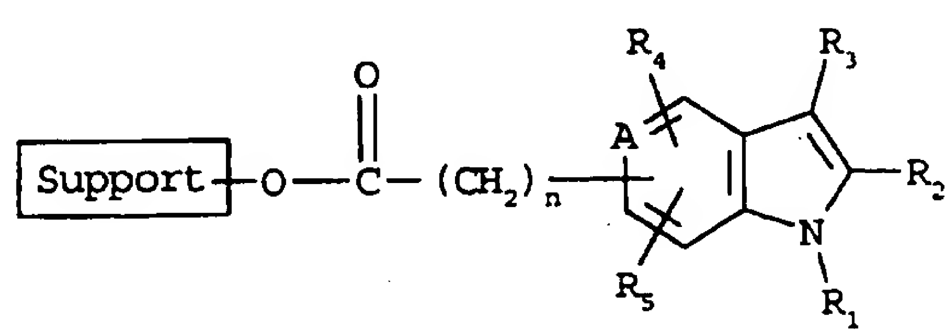
wherein R_2 and R_3 are, each independently, hydrogen or a structural diversity element;

in the presence of a transition metal as catalyst, preferably a Group VIII metal, more preferably Pd, and optionally in the presence of a Cu(I) salt, to give the indole derivatives of formula (Ia) supported on the solid support:



(Ia)

(c) optionally alkylating, acylating or sulfonylating the compounds of formula (Ia) at the nitrogen atom in position 1 to give compounds of formula (Ib):



(Ib)

wherein R_1 is a structural diversity element;

(d) optionally cleaving the compounds of formula (Ia) or (Ib) from the solid support to give the compounds of formula (I).

In formula (II), the leaving group L may be, e.g., a halogen atom, preferably bromine or iodine, or a group $-OSO_2R_9$ in which R_9 is C_1-C_6 alkyl, C_6-C_{10} aryl, C_7-C_{12} arylalkyl or alkylaryl, optionally substituted by one or more fluorine atoms, preferably R_9 is $-CF_3$ or *p*-Me-C_6H_4-. The group X is

preferably hydrogen or an activating group selected from: trifluoroacetyl, acetyl, and optionally substituted methanesulfonyl or phenylsulfonyl groups.

In formulas (I), (Ia), (Ib), (II), and (III) with "structural diversity element" it is meant any moiety which can be systematically varied to produce combinatorial libraries of compounds based on the same structural nucleus. Any of a wide variety of structural diversity elements can be used. These elements would include any accessible combination of atoms selected from carbon, hydrogen, oxygen, sulphur, nitrogen, phosphorus, silicon, and halogen (fluorine, chlorine, bromine, iodine), typically organic radicals and optionally including also alkali, alkaline-earth or transition metals. Particularly, the structural diversity elements can be selected from straight or branched alkyl, cycloalkyl, aryl, arylalkyl, or alkylaryl, heterocyclyl, heterocyclylalkyl or alkylheterocyclyl, heteroaryl, heteroarylalkyl or alkylheteroaryl groups, or any combination thereof, optionally substituted with one or more functional groups such as: cyano, nitro, halogen, hydroxy, alkoxy, carbonyl, carboxyl, amide, optionally protected amino, ester, thioester, ether, thioether, halogen (fluorine, chlorine, bromine, iodine), sulfonyl, phosphate, and the like.

The alkyl groups and alkyl moieties mentioned above may for instance be C_1-C_6 alkyl, typically C_1-C_4 alkyl, such as methyl, ethyl, i-propyl, n-propyl, t-butyl, s-butyl or n-butyl. The aryl moieties may be C_6-C_{10} aryl, for instance phenyl or naphthyl. Alkoxy may be C_1-C_6 alkoxy, typically C_1-C_4 alkoxy, such as methoxy, ethoxy, i-propoxy, n-propoxy, t-butoxy, s-butoxy or n-butoxy.

Moreover, the structural diversity elements may be selected from: natural and/or synthetic amino acid residues or oligopeptides; nucleotide derivatives, and oligonucleotides constituted by natural and/or synthetic nucleotides; carbohydrates and carbohydrate derivatives, including oligosaccharides; naturally occurring or synthetic base structures of pharmaceutically active compounds including pharmacophores or metabolites thereof; natural or synthetic macromolecular structures, including also inorganic macromolecular products; and the like.

The process of the present invention is a "solid phase synthesis" (SPS), namely a reaction carried out on macroscopic particles, made of a material insoluble in the reaction medium, to which one of the reactants is bound in a sufficient amount. The reactants are usually linked by means of reactive groups on the surface of the support, e.g. amino, carboxyl, hydroxyl or halogen groups. These reactive groups are usually already constituents of the support, however they can also be applied or modified subsequently, before the reaction. For instance, the support can be modified by treating it with a cleavable linker, namely a molecule or group of molecules which can be bound at one side to the solid substrate and at the other side to the reacting molecules, forming a spacing between solid support and synthesized molecules, and which eventually can be readily removed. Acid-cleavable linkers are described e.g. by Atherton et al, *J. Chem. Soc. Perkin I* (1981), 538-546.

The resins customarily employed in SPS can be used in the present invention, e.g. commercially available resins which

[redacted]

are usually employed in solid phase peptide synthesis or in combinatorial chemistry.

Each indole derivative may be prepared in a quantity sufficient for screening purposes, and for analysis by conventional methods, such as HPLC and mass spectral analysis, to verify purity and integrity of the obtained compound.

Step (a)

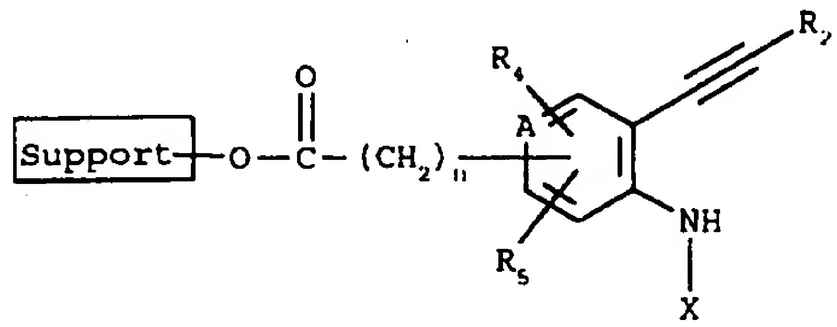
Suitable reactions for step (a) include methods which are known in the art for covalently attaching organic molecules to solid supports, such as for instance the methods described by Fruchtel and Jung, *Angew. Chem. Int. Ed. Engl.* (1996) 35: 17-42, and by Thompson and Ellman, *Chem. Rev.* (1996), 555-600. Alternatively, the compounds of formula (II) may be covalently attached to the solid support according to the Mitsunobu reaction, described in *Synthesis* (1981) pag 1, or its modified versions.

Step (b)

A wide variety of reactants of formulas (II) and (III) are known and are usually readily available from commercial suppliers, or they may be prepared according to methods known in the art, such as those described e.g. in Houben-Weil, *Methoden der Organishen Chemie*, Vol. 5/2a.

The reaction between a compound of formula (II) and a compound of formula (III) may be usually performed in an organic solvent, in the presence of a base in excess. The reaction may be carried out at a temperature of from 40° to 120°C, preferably from 60° to 100°C, for a time ranging from a few hours to several days, and preferably from four hours

to two days. When in the compounds of formula (III) R_3 is hydrogen, by using milder reaction conditions (lower temperatures and/or shorter times), intermediate products of formula:



(IV)

may be obtained, which by simple heating can be converted into the compounds of formula (Ia) having R_3 = H.

Suitable organic solvents for step (b) include, e.g., dimethylformamide (DMF), dioxane, tetrahydrofuran (THF), acetonitrile, dimethylsulfoxide, and acetone, or mixtures thereof. DMF, THF, dioxane, or mixtures thereof, are preferred. A suitable base may be, e.g., an organic base such as, mono- di- or tri-C_1-C_4-alkylamine, preferably triethylamine; a substituted C_1-C_4 alkyl guanidine, preferably tetramethylguanidine; 1,8-diazabicyclo-[5.4.0]-undec-7-ene (DBU), 1,5-diazabicyclo-[4,3,0]-non-5-ene (DBN), or 1,4-diazabicyclo-[2.2.2]-octane (DABCO), preferably DBU or DBN. Alternatively, an inorganic base may be used, such as an alkali metal or alkaline earth metal salt, e.g., $NaHCO_3$, Na_2CO_3, NaOAc, preferably Na_2CO_3, NaOAc.

The metal catalyst may be in the form of a salt or a complex with organic ligands. Particularly suitable metal catalyst are, for instance, the Group VIII metals, preferably Pd(0) complexes or a Pd(II) salt, with or without a ligand to form an organometallic complex. Preferred salts are halides and acetates, while the ligands may be selected from phosphorus-

containing compounds, e.g. triphenylphosphine (PPh_3), tri(orto)tolylphosphine ($P(o\text{-}Tol)_3$), 1,2-bis(diphenylphosphino)ethane (dppe), or 1,1-bis(diphenylphosphino)-ferrocene (dppf).

The reaction may be optionally performed in the presence of Cu(I) salts, such as, e.g., a Cu(I) halide, Cu_2O, CuCN, or a CuCN-LiCl complex, preferably CuI, CuCl, or Cu_2O.

<u>Step (c)</u>

The alkylation of the indole nitrogen atom at position 1 in compounds (Ia) may be accomplished by conventional techniques involving deprotonation of the nitrogen atom by means of a base followed by reaction with a suitable alkylating, acylating or sulfonylating agent.

Suitable bases may be selected from:

- salts of an alkali metal or alkaline earth metal, such as lithium, sodium, or potassium, with an amine, e.g. lithium diisopropylamide, or lithium bis(trimethylsylil)amide, and the like;
- an organometallic compound of an alkali metal or alkaline earth metal with an alkyl or aryl, such as butyllithium, phenyllithium, methyllithium, and tert-butyllithium;
- alkali metal or alkaline earth metal hydrides, such as NaH or KH;
- alkali metal or alkaline earth metal hydroxides or salts, such as NaOH, Na_2CO_3, KOH, K_2CO_3, $CsCO_3$, potassium tertbutylate, and the like;
- an organic base, such as: tri-C_1-C_4-alkylamine, preferably triethylamine; 1,8-diazabicyclo-[5.4.0]-undec-7-ene (DBU), 1,5-diazabicyclo-[4,3,0]-non-5-ene (DBN), or 1,4-diazabicyclo-[2.2.2]-octane (DABCO), preferably DBU or DBN.

[redacted]

The alkylating agent may be either an activated alkylating agent, such as methyl iodide or tert-butyl bromoacetate, or a non-activated alkylating agent, such as ethyl iodide or isopropyl iodide. Suitable alkylating agents include also mesylates, tosylates, and the like. The acylating agents may selected e.g. from acyl halogenides and anhydrides. The sulfonylating agents may be selected e.g. from sulfonyl chlorides and anhydrides.

The reaction is preferably carried out in a suitable organic solvent, such as, e.g., dimethylformamide (DMF), dioxane, tetrahydrofuran (THF), acetonitrile, dimethylsulfoxide (DMSO), acetone, or mixtures thereof. DMF, DMSO, THF, dioxane, or mixtures thereof, are preferably used. The reaction may be generally carried out at a temperature of from -80° to 100°C, preferably from -70° to 60°C, for a time ranging from a few minutes to several days, and preferably from one hour to one day.

Step (d)

A further element of variation may be introduced into the indole structure depending on the reactants used for the cleavage. The cleavage from the solid support may be carried out with a suitable base, such as: an inorganic base, for instance an alkali metal or alkaline earth metal hydroxide or salt, e.g., $NaHCO_3$, Na_2CO_3, NaOH, $KHCO_3$, K_2CO_3, KOH, and LiOH, preferably Na_2CO_3, NaOH, KOH, K_2CO_3 or LiOH; a nitrogen-containing base, such as ammonia, mono- or di-C_1-C_4-alkylamine. In the former case, the process yields compounds of formula (I) having R_0 equal to -OH, whereas in the latter case compounds of formula (I) having R_0 equal to $-NR_6R_7$ are obtained. By treatment with a hydroalcoholic alkaline

solution, compounds of formula (I) having R_0 equal to $-OR_8$ are obtained, wherein R_8 is different from hydrogen, possibly in admixture with the corresponding compounds having R_0 equal to -OH.

Operatively, the process object of the present invention can be carried out as follows. The resin bound substrate, prepared in a single batch as described above, is divided into equal portions in a 96-well Microtiter reaction plate. The above procedure may be performed by weighting a roughly equal amount of beads, or by making a homogeneous slurry of the resin in a suitable solvent or solvent mixture, and then adding the same volume of this slurry to each well. The reaction solvent, each different reactant, and the catalyst are then added to each individual well. The reaction plate is then stoppered and the desired reactions are then carried out, as described above. Reagents varying in their substituent groups occupy the well of each plate in a predetermined array, to achieve as ultimate products a unique indole, or if preferred a predeterminated number of indols, in each well. By using different combinations of substituents, a large number of different compounds with a common central indole structure is obtained. For example, the synthesis may begin with four different compounds of formula (II), and each of these five may be reacted with different compounds of formula (III), such as 480 different compounds of formula (III), to provide 2,400 different compounds of formula (Ia). Optional reaction of each of these 2,400 different intermediates with ten different alkylating agents according to step (c) would result in 24,000 unique indole derivatives of formula (Ib). Once formed, each indole derivative may be cleaved from the resin, as described above.

One more variation element, if desired, may be added during the cleavage, as described above. For instance, by using a water/ethanol mixture, the free acid and its ethyl ester are formed in roughly equimolar amounts. For instance, by cleaving a discrete number of unique indols a mixture of new different indole set may be generated, each well containing a mixture of different structures, each mixture distinguisheable by the substituents R_1, R_2, R_3, R_4, R_5, but not by the substituent R_0, so that each well will contain the full mixture range. More variations introduced during the cleavage would lead to an ever-increasing number of compounds.

Alternatively, the process of the present invention can be carried out analogously to the "pin method" developed by Geysen et al. for combinatorial solid-phase pepetide synthesis. A description of this method is offered for instance by Thompson and Ellman, *Chem. Rew.* (1996), 555-600. According to this method, a series of 96 pins are mounted on a block in an arrangement and spacing which correspond to a 96-well Microtiter reaction plate, and the surface of each pin is derivatised to contain terminal hydroxy or amino groups. The pin block is then lowered over a series of reaction plates in sequence to immerse the pins in the wells of the plates where coupling occurs. The various reactions are then performed as discussed above. These pins are commercially available as well as the pin blocks.

The following working examples are given to better illustrate the present invention, without being a limitation of the scope of the invention itself.

GENERAL PROCEDURE

(1) Preparation of a compound of formula (II).

A suitable aromatic amino acid (14.0 mmol) is treated with $BTMAICl_2$ (benzyltrimethylammonium dichloroiodate) (2 g) in 350 mL of CH_2Cl_2/AcOH/MeOH 3:3:1 for 4 hours at room temperature. The resulting product is then reacted with acetic anhydride (2 mL) in acetic acid (20 mL). After working up, 2 g of the compound of formula (II), wherein X = Ac, and L = I, are obtained.

(2) Coupling of the compound of formula (II) to the solid support.

Method A

The compound of formula (II) (0.4 g) is introduced into a 100 mL peptide reaction flask, along with tetrahydrofuran (THF) (50 mL), and a hydroxy resin (Tentagel™ hydroxy resin) (1.00 g) with a capacity of about 0.3-0.4 meq/g. To this mixture, an excess of Ph_3P (triphenylphosphine) and DEAD (diethylazodicarboxylate), or optionally 10 mL of a mixture of Ph_3P and DEAD in THF, are added. The mixture is vigorously shaken for 4 hours, then the solvents and excess reactants are filtered off. The resin is washed 5 times with THF, then with methanol (MeOH), and then with diethyl ether (EtO_2). The coupling cycle is optionally repeated twice, and then the resulting resin supporting the compound of formula (II) is dried in vacuum for 12 hours.

Method B

A Fmoc (fluorenylmethyloxycarbonyl) protected amino resin

[redacted]

(100 mg), having a capacity of about 0.2 meq/g, is introduced into a 10 mL peptide reaction flask. Dimethylformamide (DMF) (3 mL) and piperidine (1 mL) are added, and the resulting mixture is vigorously shaken for 1 hour, then the solvents and excess reactant are filtered off. The resin is washed 5 times with a DMF/MeOH mixture, and then dried in vacuum for 12 hours. The resulting resin is suspended in DMF (4 mL), then OHBT (hydroxybenzotriazole) (56 mg), DCC (dicyclohexylcarbodiimide) (66 mg), and the compound of formula (II) (155 mg) are added. The mixture is vigorously shaken at room temperature overnight, then the solvents and excess reactants are filtered off. The resin is washed 5 times with DMF, MeOH, and then CH_2Cl_2. The coupling cycle is optionally repeated twice, and then the resulting resin supporting the compound of formula (II) is dried in vacuum for 12 hours.

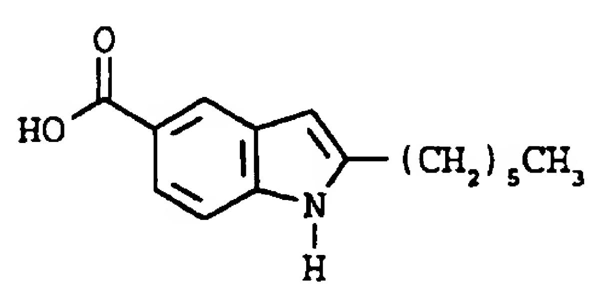
(3) Synthesis of the indole derivatives on the solid support.

The above obtained dry resin (80 mg) supporting the 3-iodo-4-aminobenzoic derivative of formula (II) in an amount of 0.2 mmol/g resin, is introduced into a round bottom flask. A compound of formula (III) is added in an amount of 50 molar equivalents with respect to the molar amount of the supported compound of formula (II), then dioxane (2 mL) and tetramethyl guanidine (2 mL) are added. $PdCl_2(PPh_3)_2$ (5.0 mg), and optionally CuI (7.0 mg), are added in sequence. The reaction flask is then stoppered and the reaction mixture is heated at 80-90°C for 24 hours, with occasional stirring. The solvent and excess reactant are then removed by filtration, and the remaining brown-yellow solid support is rinsed five times in

2 mL of dioxane, MeOH, and then diethyl ether, each washing continuing for approximately 30 sec, with filtration between successive washings. To the solid support are then added 2 mL of 2:6:0.5 *i*-PrOH/water/2N NaOH solution. The resulting mixture is heated at 40-50°C for five hours, with occasional stirring, and then left at room temperature overnight. The mixture is then filtered to remove the solid support. The solid support is then rinsed three times with 3 mL of an isopropanol/water mixture. The solution is evaporated, and the residual water solution is acidified with diluted HCl. Extraction with ethyl acetate (EtOAc) and concentration of the combined extacts then provides the indole derivatives of formula (Ia). The final basic cleavage may be performed using MeOH/water or EtOH/water mixtures so affording the corresponding esters of formula (I).

Following the above described general procedure, the following indole derivatives were prepared:

<u>2-(n-hexyl)-indole-5-carboxylic acid</u>



^1H NMR ($CDCl_3$) δ (ppm): 8.37 (1H, d, J = 1.8 Hz); 8.09 (1H, br s); 7.90 (1H, m); 7.32 (1H, m); 6.35 (1H, m); 2.78 (2H, t, J = 7.4 Hz); 0.9-1.8 (11H, m).

Ms (EI): 245 ($M^{+\cdot}$); 188 ($M-C_4H_9$); 174 (100%, $M-C_5H_{11}$).

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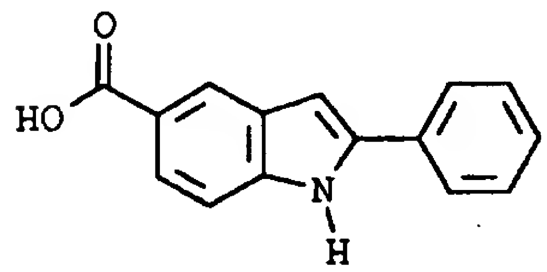
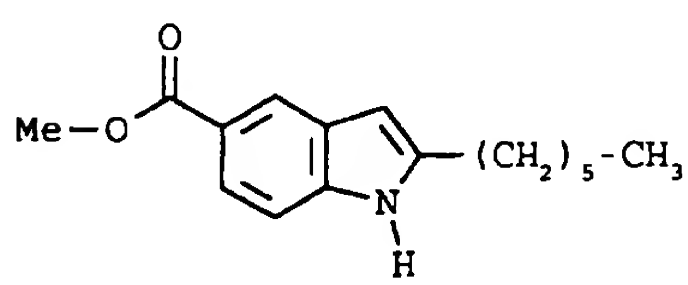
2-phenyl-indole-5-carboxylic acid



^1H NMR ($CDCl_3$) δ (ppm): 8.47 (1H, d, J = 1.8 Hz); 7.96 (1H, m); 7.68 (1H, m); 7.3-7.5 (5H, m); 6.93 (1H, m).

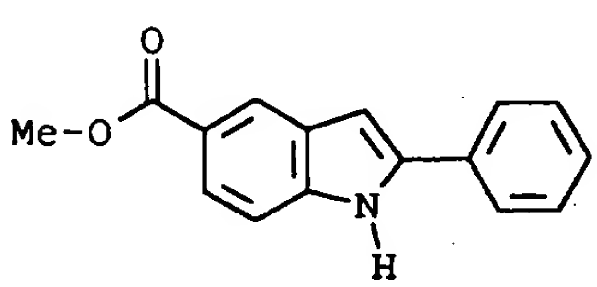
Ms (EI): 237 (100%, $M^{+\cdot}$); 220 (M-OH); 192 (M-COOH).

2-(*n*-hexyl)-indole-5-carboxylic acid, methyl ester



^1H NMR ($CDCl_3$) δ (ppm): 8.28 (1H, d, J = 1.8 Hz); 8.1 (1H, br s); 7.83 (1H, m); 7.29 (1H, m); 6.32 (1H, m); 3.92 (3H, s); 2.80 (2H, t, J = 7.4 Hz); 0.9-1.7 (11H, m).

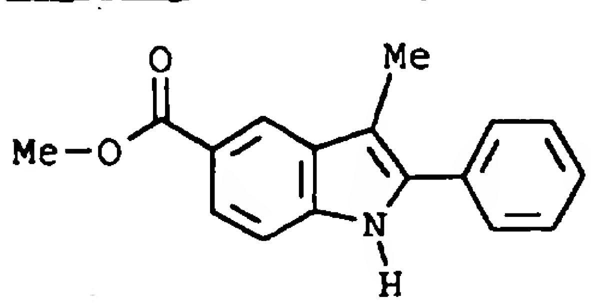
2-phenyl-indole-5-carboxylic acid, methyl ester



^1H NMR ($CDCl_3$) δ (ppm): 8.54 (1H, br s); 8.39 (1H, s); 7.91 (1H, m); 7.68 (1H,m); 7.3-7.5 (5H, m); 6.91 (1H, m); 3.94 (3H, s).

Ms (EI): 251 (100%, $M^{+\cdot}$); 220 ($M-OCH_3$); 192 ($M-COOCH_3$).

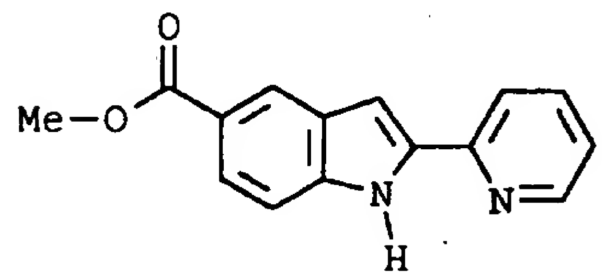
2-phenyl-3-methyl-indole-5-carboxylic acid, methyl ester



^{1}H NMR (DMSO-d_6) δ (ppm): 12.42 (1H, br s); 8.76 (1H, m); 7.4-7.9 (7H, m); x.xx (3H, ?); 3.86 (3H,s).

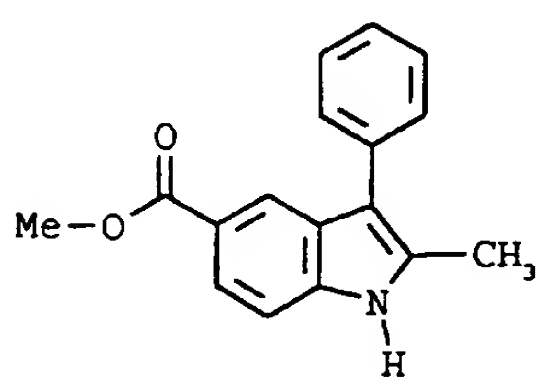
Ms (EI): 365 (100%, $M^{+\cdot}$); 234 ($M-OCH_3$).

<u>2-(2-pyridyl)-indole-5-carboxylic acid, methyl ester</u>



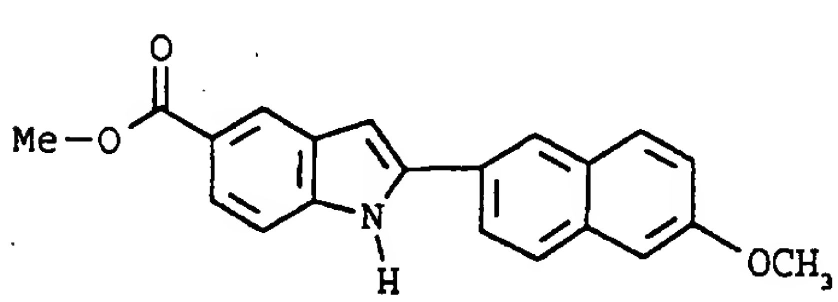
^{1}H NMR (DMSO-d_6) δ (ppm): 12.03 (1H, s); 8.64 (1H, ddd); 8.28 (1H, d); 8.01 (1H, ddd); 7.87 (1H, ddd); 7.75 (1H, dd); 7.53 (1H, d); 7.28-7.38 (2H, m); 3.82 (3H, s).

<u>2-methyl-3-phenyl-indole-5-carboxylic acid, methyl ester</u>



^{1}H NMR (DMSO-d_6) δ (ppm): 11.53 (1H, s); 8.15 (1H, d); 7.70 (1H, dd); 7.40 (1H, d); 7.24-7.54 (5H, m); 3.80 (3H, s); 2.45 (3H, s).

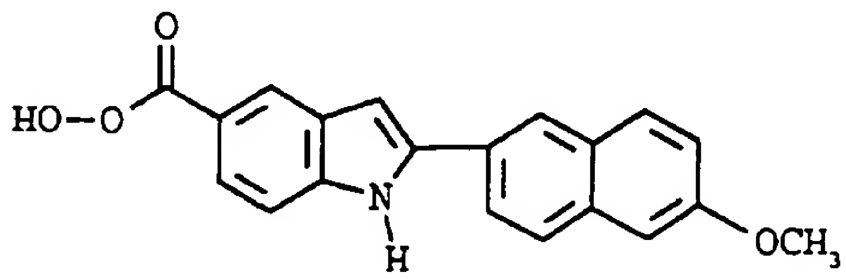
<u>2-(6-methoxy-naphthyl-2-yl)-indole-5-carboxylic acid, methyl ester</u>



^{1}H NMR (DMSO-d_6) δ (ppm): 12.02 (1H, bs); 8.31 (1H, d); 8.24 (1H, d); 7.97 (1H, dd); 7.90 (1H, d); 7.85 (1H, d); 7.73 (1H, dd); 7.48 (1H, d); 7.35 (1H, d); 7.20 (1H, dd); 7.12

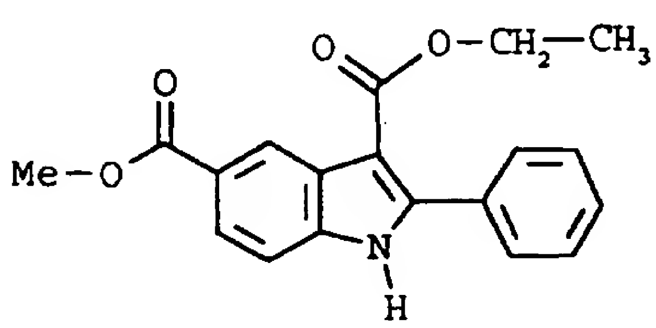
(1H, d); 3.88(3H, s); 3.84 (3H, s).

<u>2-(6-methoxy-naphthyl-2-yl)-indole-5-carboxylic acid</u>



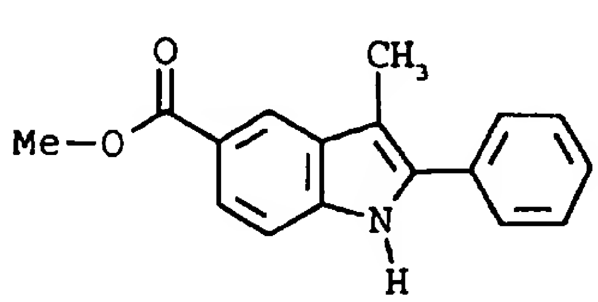
^{1}H NMR ($CDCl_3$) δ (ppm): 12.37 (1H, bs); 11.93 (1H, s); 8.28 (1H, d); 8.17 (1H, d); 7.94 (1H, dd); 7.86 (1H, d); 7.81 (1H, d); 7.68 (1H, dd); 7.42 (1H, d); 7.31 (1H, d); 7.17 (1H, dd); 7.07 (1H, d); 3.85 (3H, s).

<u>3-ethoxycarbonyl-2-phenyl-indole-5-carboxylic acid, methyl ester</u>



^{1}H NMR (DMSO-d_6) δ (ppm): 12.42 (1H, s); 8.76 (1H, d); 7.83 (1H, dd); 7.67-7.71 (2H, m); 7.47-7.54 (4H, m); 4.20 (2H, q); 3.86 (3H, s); 1.19 (3H, t).

<u>3-methyl-2-phenyl-indole-5-carboxylic acid, methyl ester</u>



^{1}H NMR (DMSO-d_6) δ (ppm): 11.53 (1H, s); 8.21 (1H, d); 7.74 (1H, dd); 7.36-7.70 (5H, m); 7.41 (1H, d); 3.84 (3H, s); 2.43 (3H, s).

(4) Synthesis of a library of indole derivatives.

The above prepared dry resin (1.2 g), supporting the substituted 3-iodo-4-aminobenzoic derivative of formula (II) in an amount of 0.2 mmol/g resin, is divided into 96 portions having roughly the same weight, and each portion is added to a well of a Microtiter 96-well polypropylene plate. A compound of formula (III) is added in inert atmosphere in an amount of 50 mole equivalents with respect to the molar amount of the supported compound of formula (II). Then a solution of dioxane (0.3 mL) and tetramethyl guanidine (0.3 mL), containing $PdCl_2(PPh_3)_2$ (0.8 mg), and optionally CuI (1.1 mg), are added in inert atmosphere. Each well is then stoppered and the reaction plate is heated at 80-90°C for 24 hours in an oven, with occasional stirring. The solvent and excess reactant is then removed by filtration from each well, and the remaining brown-yellow solid support is rinsed five times in 1 mL of dioxane, and then 1 mL of MeOH, each washing lasting approximately 30 sec, with filtration between successive washings. To the solid support in each well are then added 0.6 mL of 2:6:0.5 *i*-PrOH/water/2N NaOH solution. The resulting mixture is heated at 40-50°C for five hours, with occasional stirring, and then left at room temperature overnight. Each well is then filtered to remove the solid support. The solid support is then rinsed three times with 0.5 mL of an *i*-PrOH/water mixture. The solution is evaporated by using, e.g., an oven or other commercial equipment, such as a Microtiter plate speed vacuum apparatus, then the pH of the residual water solution is adjusted to about 7 with 2N HCl. Concentration as above then provides the products of formula (I) in the dry form.

Alternatively, the final alkaline cleavage may be performed

by using MeOH/water or EtOH/water mixtures, so affording the corresponding esters of formula (I).

(5) Screening.

After evaporation of the solvents, as described above, the screening may be performed by any of the standard methods for performing screens on Microtiter plates. For instance, the methods described by Geysen et al. in *J. Immunobiological Methods* (1987) 102: 259-274, can be employed, if the case suitably modified to fit the tested compounds.

EXAMPLE 1

Following the general procedure described above and using ethanol in the final cleaving step, an array of indole molecules was generated as reported in the following Table I.

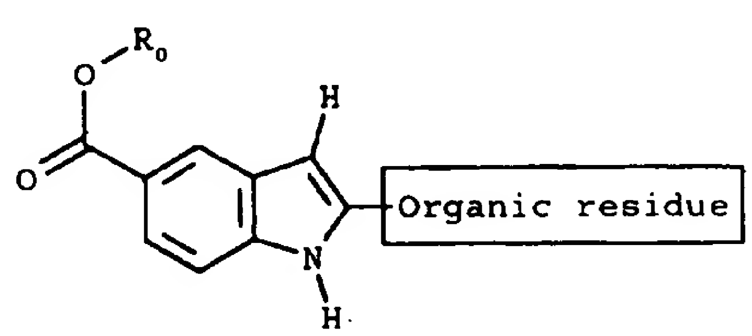


TABLE I

Organic Residue	R_0	Organic Residue	R_0
$(CH_2)_2$-CH_3	H	$(CH_2)_2$-CH_3	Et
CH_2-cyclopentyl	H	CH_2-cyclopentyl	Et
Ph	H	Ph	Et
p-CH_3-Ph	H	*p*-CH_3-Ph	Et
p-CH_3O-Ph	H	*p*-CH_3O-Ph	Et
$(CH_2)_3$-Cl	H	$(CH_2)_3$-Cl	Et
p-Cl-Ph	H	*p*-Cl-Ph	Et

EXAMPLE 2

Following the general procedure described above and using ethanol in the final cleaving step, an array of indole molecules was generated as reported in the following Table II.

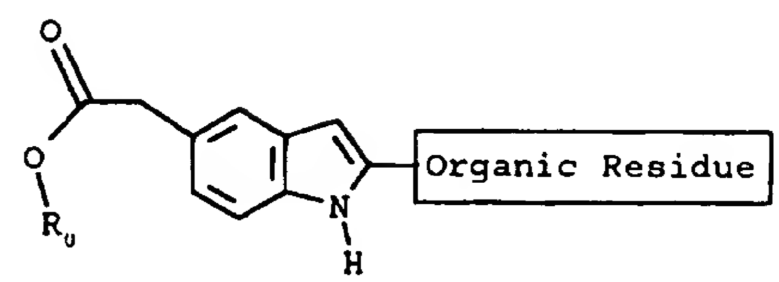


TABLE II

Organic Residue	R_0	Organic Residue	R_0
$(CH_2)_8-CH_3$	H	$(CH_2)_8-CH_3$	Et
CH_2-cyclopentyl	H	CH_2-cyclopentyl	Et
Ph	H	Ph	Et
p-CH_3-Ph	H	*p*-CH_3-Ph	Et
p-CH_3O-Ph	H	*p*-CH_3O-Ph	Et
$(CH_2)_4-OH$	H	$(CH_2)_4-OH$	Et
$CH_2-N(CH_3)_2$	H	$CH_2-N(CH_3)_2$	Et
$(CH_2)_3-Cl$	H	$(CH_2)_3-Cl$	Et

EXAMPLE 3

Following the general procedure described above and using methanol in the final cleaving step, an array of indole molecules was generated as reported in the following Table III.

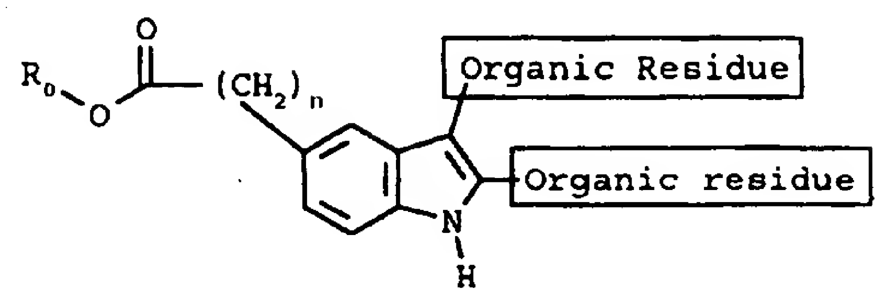
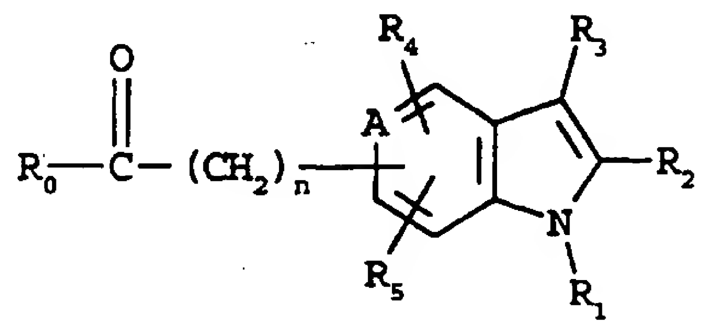


TABLE III

Organic Residue	Organic Residue	n	R_0
Ph	Me	0	H
Ph	Me	0	Me
Ph	Me	1	H
Ph	Me	1	Me
Me	Ph	0	H
Me	Ph	0	Me
Me	Ph	1	H
Me	Ph	1	Me
Me	*n*-Bu	0	H
Me	*n*-Bu	0	Me
Me	*n*-Bu	1	H
Me	*n*-Bu	1	Me
n-Bu	Me	0	H
n-Bu	Me	0	Me
n-Bu	Me	1	H
n-Bu	Me	1	Me

CLAIMS

1. A process for producing a plurality (library) of indole derivatives of formula:



(I)

wherein:

R_1, R_2, R_3, R_4, and R_5, which are the same or different, are each hydrogen or a structural diversity element, with the proviso that at least one of R_1, R_2, R_3, R_4, and R_5 is different from hydrogen;

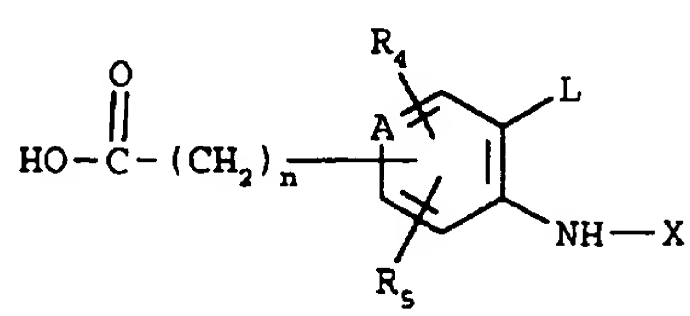
R_0 is $-NR_6R_7$ or $-OR_8$, wherein R_6, R_7, and R_8, which are the same or different, are each hydrogen or a structural diversity element;

A is CH or N, and may occupy any of the unsubstituted positions of the phenyl ring; and

n is zero or an integer from 1 to 4;

which process comprises the steps of:

(a) coupling to a solid support a first scaffold of formula:



(II)

wherein:

R_4 and R_5, which are the same or different, are each hydrogen or a structural diversity element;

A is CH or N, and may occupy any of the unsubstituted positions of the phenyl ring;

n is zero or an integer from 1 to 4;

L is a leaving group; and

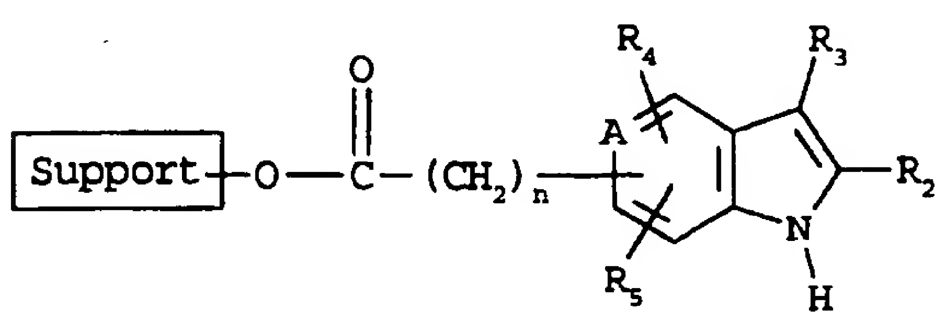
X is hydrogen or an activating group;

(b) reacting said first scaffold coupled to the solid support with a second scaffold of formula:

$$R_2 - \equiv - R_3 \qquad (III)$$

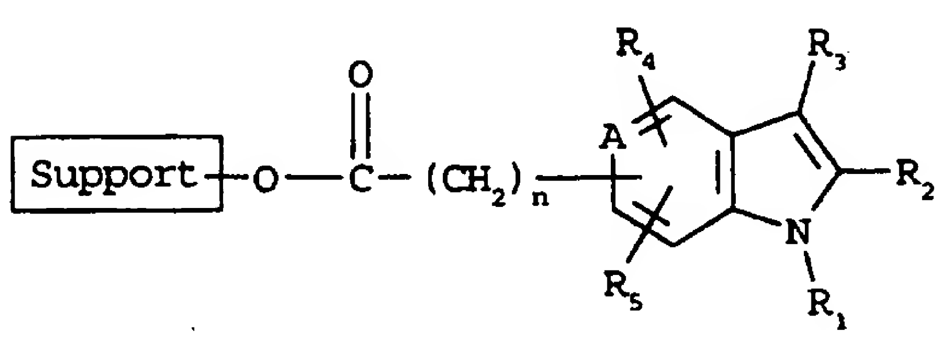
wherein R_2 and R_3, which are the same or different, are each hydrogen or a structural diversity element;

in the presence of a transition metal as catalyst, and optionally in the presence of a Cu(I) salt, to give indole derivatives of formula (Ia) supported on the solid support:



(Ia)

(c) optionally alkylating, acylating or sulfonylating the said derivatives of formula (Ia) at the nitrogen atom in position 1 to give indole derivatives of formula (Ib):



(Ib)

wherein R_1 is a structural diversity element;

(d) optionally cleaving the said derivatives of formula (Ia) or (Ib) from the solid support to give indole derivatives of formula (I).

2. A process according to claim 1, wherein in formula (II) the leaving group L is a halogen atom or a group $-OSO_2R_9$ in which R_9 is C_1-C_6 alkyl, C_6-C_{10} aryl, C_7-C_{12} arylalkyl or alkylaryl, optionally substituted by one or more fluorine atoms.

3. A process according to claim 1, wherein in formula (II) X is an activating group selected from trifluoroacetyl, acetyl, and optionally substituted methanesulfonyl or phenylsulfonyl groups.

4. A process according to claim 1, wherein in step (b) the catalyst is a Group VIII metal.

5. A process according to claim 4, wherein in step (b) the catalyst is a Pd(0) complex or a Pd(II) salt, with or without a ligand to form an organometallic complex.

6. A process according to claim 1, wherein step (b) is carried out in an organic solvent, in the presence of a base in excess.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 97/02600

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D209/08

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07D C07B

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	LAROCK, RICHARD C. ET AL: "Synthesis of indoles via palladium -catalyzed heteroannulation of internal alkynes" J. AM. CHEM. SOC. (1991), 113(17), 6689-90 CODEN: JACSAT;ISSN: 0002-7863, 1991, XP002041638 ---	1-6
A	SAKAMOTO, TAKAO ET AL: "Condensed heteroaromatic ring systems. XIII. One-step synthesis of 2-substituted 1-methylsulfonylindoles from N-(2-halophenyl)methanesulfonamides" CHEM. PHARM. BULL. (1988), 36(4), 1305-8 CODEN: CPBTAL;ISSN: 0009-2363, 1988, XP002041639 ---	1-6

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[X] Further documents are listed in the continuation of box C.

[ ] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier document but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
"&" document member of the same patent family

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Date of the actual completion of the international search	Date of mailing of the international search report
24 September 1997	02.10.97

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	De Jong, B

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Int ional Application No
PCT/EP 97/02600

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	ARCADI, ANTONIO ET AL: "A versatile approach to 2,3-disubstituted indoles through the palladium -catalyzed cyclization of o-alkynyltrifluoroacetanilides with vinyl triflates and aryl halides" TETRAHEDRON LETT. (1992), 33(27), 3915-18 CODEN: TELEAY;ISSN: 0040-4039, 1992, XP002041640 ---	1-6
A	YU, KUO-LONG ET AL: "Heck reactions in solid phase synthesis" TETRAHEDRON LETT. (1994), 35(48), 8919-22 CODEN: TELEAY;ISSN: 0040-4039, 1994, XP002041641 ---	1-6
T	FAGNOLA, MARIA CHIARA ET AL: "Solid-phase synthesis of indoles using the palladium -catalyzed coupling of alkynes with iodoaniline derivatives" TETRAHEDRON LETT. (1997), 38(13), 2307-2310 CODEN: TELEAY;ISSN: 0040-4039, 1997, XP002041642 -----	1-6

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